PTO/SB/21 (09-04)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	08/889,355
Filing Date	July 8, 1997
First Named Inventor	Heidrun Engler
Art Unit	1632
Examiner Name	Michael C. Wilson
Attorney Docket Number	016930-000811US

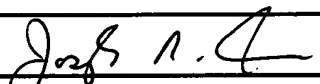
Total Number of Pages in This Submission

ENCLOSURES *(Check all that apply)*

- ☒ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please identify below):
  Return Postcard

Remarks: The Commissioner is authorized to charge any additional fees to Deposit Account 20-1430.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Townsend and Townsend and Crew LLP		
Signature			
Printed name	Joseph R. Snyder		
Date	May 2, 2005	Reg. No.	39,381

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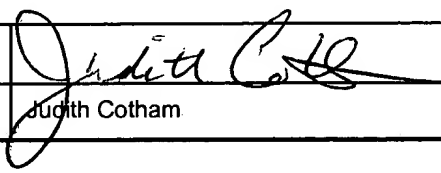
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Signature			
Typed or printed name	Judith Cotham	Date	May 2, 2005

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 500

Complete if Known	
Application Number	08/889,355
Filing Date	July 8, 1997
First Named Inventor	Heidrun Engler
Examiner Name	Michael C. Wilson
Art Unit	1632
Attorney Docket No.	016930-000811US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 20-1430 Deposit Account Name: Townsend and Townsend and Crew LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____	-20 or HP = _____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____	-3 or HP = _____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____ / 50 =	_____ (round up to a whole number) x	_____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other: Filing a brief in support of an appeal	500

SUBMITTED BY

Signature	Joseph R. Snyder	Registration No. (Attorney/Agent) 39,381	Telephone 925-472-5000
Name (Print/Type)	Joseph R. Snyder		Date May 2, 2005

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AF/CPW/1632

PATENT
Attorney Docket No.: 016930-000811US
Client Ref. No.: 3013B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Heidrun Engler et al.

Application No.: 08/889,355

Filed: July 8, 1997

For: COMPOSITIONS AND METHODS FOR THERAPEUTIC USE

Customer No.: 20350

Confirmation No. 3379

Examiner: Michael C. Wilson

Technology Center/Art Unit: 1632

APPEAL BRIEF UNDER 37 CFR § 41.37

Board of Patent Appeal and Interferences
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action mailed November 2, 2004 for the above-captioned application and further to the Notice of Appeal filed March 2, 2005, Appellants submit the following appeal brief under 37 CFR § 41.37. Please deduct the requisite fee pursuant to 37 CFR § 41.20(b)(2) of $500.00 from deposit account 20-1430.

05/05/2005 FMETEKI1 00000015 201430 08889355
01 FC:1402 500.00 DA

I. REAL PARTY OF INTEREST

Canji Inc. and Schering Corporation are the real parties of interest as the co-assignees of the above-identified application.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known that will directly affect or be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 41 and 54-55 are pending in the application. Claims 41 and 55 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. Claims 41 and 55 stand rejected under 35 U.S.C § 112 second paragraph, for allegedly being indefinite. Claims 54 and 56 were again withdrawn by the Examiner in the most recent Office Action as allegedly not being drawn to the present invention. Claim 56 has been canceled. Claims 1-40 and 42-53 were previously canceled. The subject matter of claims 41 and 55 are at least twice rejected. Therefore, claims 41 and 55 are appealed. In addition, Appellants submit that claim 54 sets forth a specific compound that is within the elected invention. As such, Appellants respectfully request that claim 54 be rejoined and examined on its merits. Claims 41 and 54-55 as presently constituted are set forth in Appendix A.

IV. STATUS OF AMENDMENTS

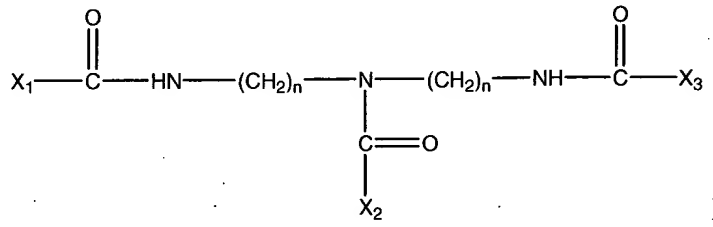
With respect to claims 41 and 54-55, Appellants filed an Amendment on July 9, 2004 seeking to overcome certain § 112 rejections set out in the Office Action dated January 16, 2004. All previous amendments have been entered

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention provides novel compounds, referred to as "delivery-enhancing agents," that advantageously enhance the delivery of therapeutic or diagnostic agents to a cell or tissue (*see*, specification at page 7, lines 17-20). The therapeutic and diagnostic agents that can be delivered using the delivery-enhancing agents of the invention are proteins and

nucleic acids, including gene therapy vectors (*see*, specification on page 10, lines 7-16; and Example 5).

Certain preferred embodiments of delivery-enhancing agents have the structure of Formula I as shown below:



I

in which "n" is an integer from 2-8, X_1 is a cholic acid group or deoxycholic acid group, and X_2 and X_3 are independently selected from the group consisting of a cholic acid group, a deoxycholic acid group, and a saccharide group; wherein at least one of X_2 and X_3 is a saccharide group (*see*, specification on page 9, lines 1-11). The saccharide groups may be a pentose monosaccharide group, a hexose monosaccharide group, a pentose-pentose disaccharide group, a hexose-hexose disaccharide group, a pentose-hexose disaccharide group and a hexose-pentose disaccharide group (*see*, specification on page 9, lines 11-14).

The appealed claims are drawn to preferred delivery-enhancing agents of the inventions. Claim 41 is directed toward an embodiment of Formula I in which "n" is 3, X_1 and X_2 are cholic acid groups, and X_3 is a pentose saccharide group (*see*, specification on page 9, lines 14-23; original claims 42 and 45). Claim 54 is drawn to a compound, 3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide, which is a species within the genus of Formula I as presently claimed (*see*, Example 12). Claim 55 is directed toward an embodiment of Formula I in which "n" is 3, X_1 and X_2 are cholic acid groups, and X_3 is a hexose saccharide group (*see*, specification on page 9, lines 14-23; original claim 48).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The two issues on appeal are:

I. Whether claims 41 and 55 meet the requirement of 35 U.S.C. § 112, first paragraph. Specifically, with regard to this issue, i) whether the specification adequately describes the delivery-enhancing agent subgenus as recited in claims 41 and 55, and more

particularly, whether the specification adequately describes the structure of Impurity II as a compound having the subgenus as recited in claim 41; ii) whether the specification adequately describes the manner in which a cholic acid group is attached to Formula I; and iii) whether undue experimentation would be required to make or use the compound of Impurity II.

II. The second issue is whether claims 41 and 55 meet the requirement of 35 U.S.C. § 112, 2nd paragraph. Specifically, the issue is whether the structures encompassed by the claims are clear, in particular with reference to the use of the term "cholic acid group".

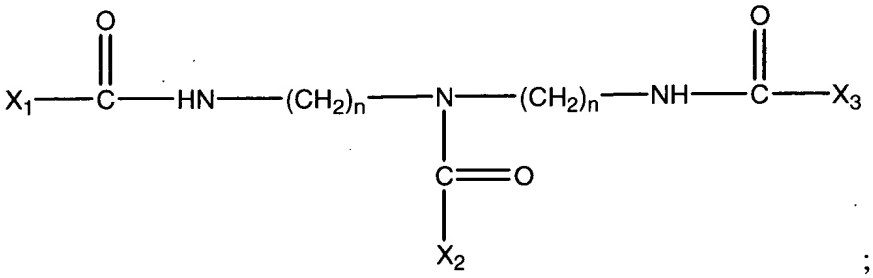
VII. ARGUMENT

A. The rejection for lack of written description is improper.

As will be discussed in detail below, the present application fully complies with the written description requirement under 35 U.S.C. § 112, first paragraph. Appellants submit that the written description rejection is improper and should be withdrawn.

1. A summary of the claimed composition.

The pending claims are directed to a delivery-enhancing compound having formula I:



;

in which n is 3, X_1 and X_2 are both cholic acid groups, and X_3 is a pentose monosaccharide (Claim 41) or a hexose monosaccharide (Claim 55). Claim 54 is drawn to a species within the scope of Formula I as presently claimed.

2. Brief summary of the prosecution history and the Patent Office's rationale.

The Patent Office rejected the original presentation of claim 41 stating that the specification does not adequately described the structure of Impurity II, and therefore claiming all the compounds within the genus of claim 41 without describing the specific structure of one compound within the genus is not in compliance with the description requirement (*see*, Office

Action of April 23, 2003, pages 3 and 4). Appellants amended claim 41 to focus on a subgenus of compounds around the structure of Impurity II, (*i.e.*, compounds of Formula I wherein X_1, X_2 are cholic acid groups and X_3 is a pentose monosaccharide). For support of the amended subgenus, Appellants respectfully pointed out to the Office that the structure of Impurity II is described by the synthetic scheme presented in Example 12 of the specification (*see*, Amendment of October 17, 2003, page 6). Appellants also provided evidence to show that the synthetic intermediates and the final product formed following the experimental procedures outlined in Example 12 are based on common synthetic transformations that can be found in an introductory organic textbook, and as such, the intermediates and the final product from Example 12 would be easily recognized by a skilled artisan (*see*, Amendment of July 9, 2004, page 7). In addition, Appellants also set forth a claim drawn to the disclosed species, 3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide, that was prepared in Example 12 (*see*, claim 54).

The Patent Office is of the opinion that the specification does not teach that the compound synthesize in Example 12 (3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide) is Impurity II (*see*, Office Action of January 16, 2004, page 5). Thus, the Office alleges that it is not clear that the product of Example 12 is related to the claimed genus (*see*, Office Action of January 16, 2004, page 2). Moreover, the Office is of the opinion that a skilled artisan would not know what compound is prepared by the synthetic procedure outlined in Example 12, specifically with regard to how the cholic acid group would be attached at the X_1 and X_2 positions of Formula I (*see*, Office Action of January 16, 2004, page 5).

The issue at hand is whether the specification describes the delivery-enhancing agent subgenus as presented in claims 41 and 55, and more particularly, whether the specification describes: 1) the structure of Impurity II as a compound having the subgenus as presented in the claims; and 2) the structure of the cholic acid group when attached to Formula I.

3. Example 12 teaches unequivocally the structure of Impurity II.

The Office alleges the structure of Impurity II was only determined in a later filed application (U.S. Ser. No. 09/112,074 now U.S. 6,392,069) (*see*, Office Action of November 2, 2004, pages 4 and 5). Appellants respectfully disagree. For the reasons set forth below,

Appellants assert that the structure and synthesis of Impurity II are taught by the original specification.

The specification teaches that the impurities of Big CHAP from CalBiochem enhance the delivery of therapeutic agents. As evidence, Appellants refer the Board's attention to Figure 20 of the specification which describes the gene delivery enhancing results using **pure** Big CHAP, purchased from SIGMA, that was spiked with the isolated impurities from Big CHAP that was purchased from CalBiochem. In particular, it was found that a specific impurity, Impurity II, was very effective at enhancing gene delivery. **The specification discloses that to confirm the structure of Impurity II, Impurity II was also synthesized.** Appellants respectfully direct the Board's attention to the lower right panel of Figure 20[1] which shows that spiking **pure** Big CHAP from SIGMA with **synthesized Impurity II** resulted in enhanced gene transfer. For the Board's convenience, a copy of Figure 20 from the application is attached as Appendix B1. Appellants respectfully assert that the specification (Figure 20) clearly teaches that Impurity II was **synthesized** in addition to being isolated from CalBiochem Big CHAP. **The teaching in the specification that Impurity II was synthesized, provides clear evidence that Appellants were in possession of the structure of Impurity II at the time of filing.**

The specification clearly discloses Impurity II as being synthesized thus there is no ambiguity that the synthetic procedure outlined in Example 12 of the specification, corresponds to the synthetic procedure for making the compound Appellants disclosed as being Impurity II. Thus, Appellants respectfully assert that the specification teaches that Impurity II was synthesized and that the synthesis of Impurity II is presented in Example 12.

4. The attachment of a cholic acid group is defined in Example 12.

The Patent Office also alleges that the structure of the cholic acid group as presented in claims 41 and 55 does not have support in the original specification. More particularly, the Office alleges that the manner in which the cholic acid group is attached at the X_1 and X_2 positions in Formula I was not disclosed in the original specification. Appellants respectfully disagree. For the reasons set forth below, Appellants respectfully assert that the

[1] See Appendix B1, lower right panel.

structure of Impurity II and the manner in which the cholic acid groups are attached in Impurity II is clear in the specification.

Example 12 describes the synthesis of 3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide which is Impurity II. Appellants submit that the chemical structure of the final product, Impurity II, and the intermediates leading to the final product would be readily apparent to one skilled in the art.

For example, in Step 1 of Example 12, the specification teaches that one equivalent of glucono-δ-lactone is reacted with one equivalent of iminobispropylamine to form the amide product, 3-aminopropyl-3'-N-glucoamidopropyl-amine. The reagents specified in Step 1 are commercially available and would be known to a skilled artisan. As such, Appellants respectfully submit that one skilled in the art would immediately recognize that the reaction of the glucono-δ-lactone with iminobispropylamine will form the *amide* product 3-aminopropyl-3'-N-glucoamidopropyl-amine as shown in Figure 1.

Figure 1:

Iminobispropylamine Glucono-δ-lactone 3-Aminopropyl-3'-N-gluconamidopropyl-amine

Furthermore, referring to Step 2 of Example 12, Appellants assert that one skilled in the art would immediately recognize that the reaction of the cholic acid (a carboxylic acid) starting material with isobutylchloroformate (an acid chloride derivative) will form a mixed anhydride intermediate (*see*, Figure 2 below). As an aside, Appellants note that *iso*-butylchloroformate and cholic acid are both commercial reagents, the structures of which would be readily apparent to a skilled artisan. Subsequent reaction of the mixed anhydride intermediate with 3-aminopropyl-3'-N-glucoamidopropyl-amine (an amine), will result in the formation of the amide bonds of Impurity II in which the carbonyl group of the amide group will have originated from the cholic acid starting material as depicted below in Figure 3 below.

Figure 2:

Synthesis of the "Mixed Anhydride"

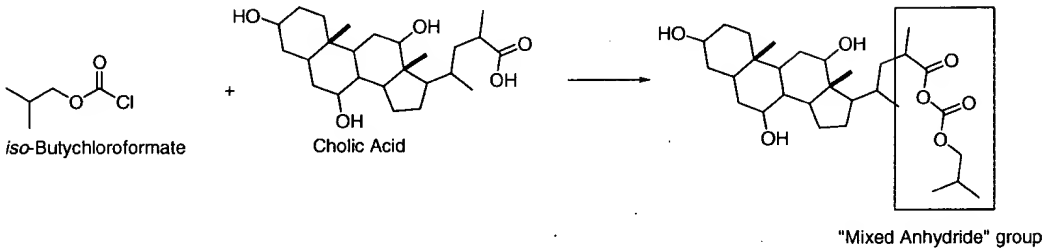
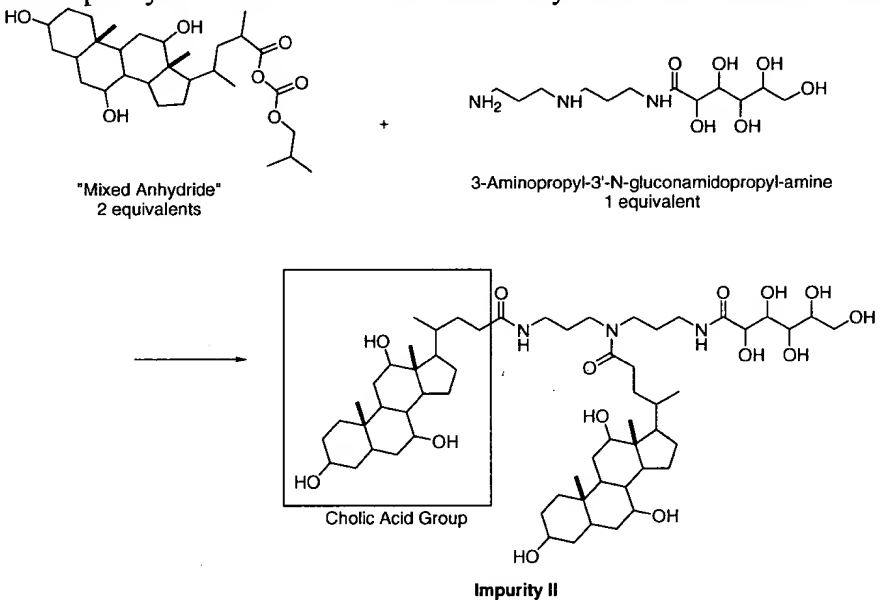


Figure 3:

Synthesis of Impurity II: Reaction of the mixed anhydride with the amine from Step 1.



In this instance, Appellants also submit that the chemical reactions used in Example 12 are common synthetic transformations well known to one skilled in the art as shown by the fact that an analogous set of transformations is described in the introductory organic textbook titled "Introduction to Organic Chemistry".[2] The following reactions are described therein: 1) the reaction of an acid chloride derivative and a carboxylic acid to form an anhydride; and 2) the reaction of an anhydride with an amine. Relevant sections from the textbook are reproduced in Figures 4 and 5 (below) for the Board's convenience.

Figure 4: Reaction of an acid chloride with a carboxylic acid.

[2] See Appendix B2. Introduction to Organic Chemistry, 4th Ed.; 1992; Prentice-Hall, Inc., pgs. 530-531.

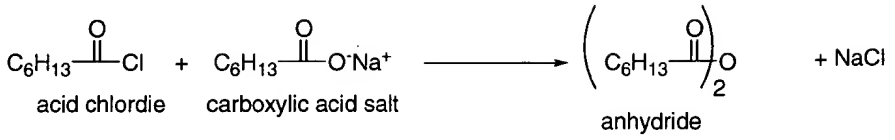
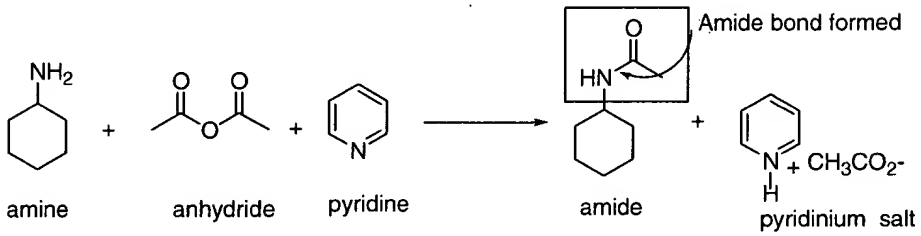


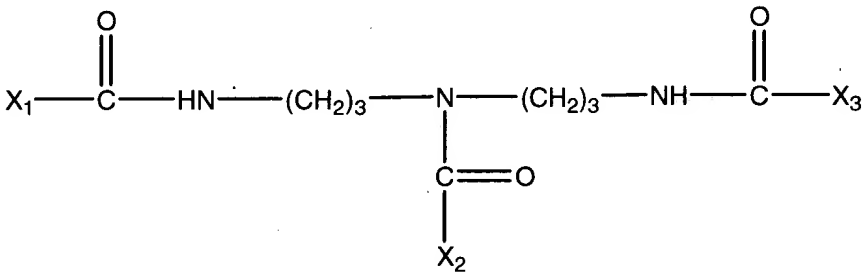
Figure 5: Reaction of an anhydride with an amine.



As such, based on the experimental procedure (*i.e.*, reagents used and the description of the resultant intermediates) provided in Example 12, Appellants assert that a skilled artisan attempting to practice the present invention would readily recognize the chemical structures of the intermediates and more importantly, the structure of Impurity II and the manner of attachment of the cholic acid group therein. In view of the above, Appellants submit that the original specification teaches how a cholic acid group is attached to a compound of Formula I. The statutory requirements of 35 U.S.C. § 112 require no more.

5. The specification supports the claimed genus.

Claim 41 and claim 55 are amended to focus on a preferred embodiment of the invention, in which in a compound having Formula I, the X_1 and X_2 groups are both cholic acid groups and the X_3 group is a pentose or a hexose monosaccharide, respectively. Appellants submit that support for the amended genus is found in the specification as originally filed. The specification, on page 5, lines 2 to 10, describes that the preferred compounds of the invention have the formula shown below:



in which X_1 and X_2 are independently either a cholic acid group or deoxycholic acid group, and X_3 is a saccharide group. In addition, the preferred embodiment is also set forth in original claims, 43 and 48 (see below).

> Claim 43: The compound of claim 41, wherein both ***X_1 and X_2 are both cholic acid groups*** and ***X_3 is a saccharide***.
>
> Claim 48: The compound of claim 41, wherein n is 3, ***X_1 and X_2 are both cholic acid groups***, and ***X_3 is a hexose monosaccharide group***.

Furthermore, the specification teaches how to make and use a species (Impurity II) that is within the genus of the compounds as presently claimed. For example, Example 11 of the specification teaches how to isolate Impurity II. Figure 20 shows that Impurity II was both isolated **and** synthesized; and that both the isolated and synthesized forms of Impurity II enhanced gene transfer to the same extent. Example 12 of the specification describes the structure of Impurity II by providing a detailed synthetic procedure for making Impurity II.

In view of the description provided in the specification, Appellants submit that the original disclosure provides full support for the subject matter of the instantly claimed genus of compounds of Formula I in which X_1 and X_2 are cholic acid groups and X_3 is a pentose or hexose monosaccharide.

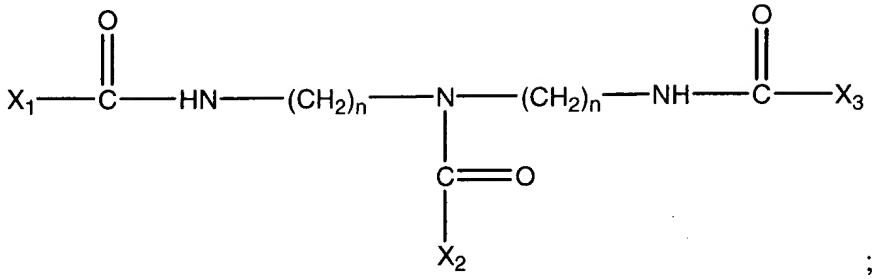
In view of the above, Appellants respectfully request that the written description rejection be withdrawn.

B. The rejection for lack of enablement is improper.

As will be discussed in detail below, the present application fully complies with the enablement requirement as set forth under 35 U.S.C. § 112, first paragraph. Appellants submit that the enablement rejection is improper and should be withdrawn.

1. A summary of the claimed composition.

The claims on appeal are directed to delivery-enhancing compounds having Formula I:



;

in which n is 3, X_1 and X_2 are both cholic acid groups, and X_3 is a pentose monosaccharide (Claim 41) or a hexose monosaccharide (Claim 55). Claim 54 is drawn to a species within the scope of Formula I as presented in Claim 41.

2. Brief summary of the prosecution history and the Patent Office's rationale.

Briefly summarized here, the Patent Office rejected the original presentation of claim 41 as allegedly not being enabled. It was the opinion of the Office that the genus of compounds embodied by claim 41 was non-enabled as allegedly the specification did not provide examples of compounds having the breadth of X_1, X_2 and X_3 groups as claimed (*see,* Office Action of July 23, 2003, page 9). In order to expedite prosecution, Appellants responded by focusing the subject matter of claim 41 to a preferred embodiment of the delivery-enhancing agents based on Impurity II. For example, the claims were amended to recite a compound of Formula I, wherein n is 3, X_1 and X_2 are cholic acid groups and X_3 is a pentose monosaccharide (*see*, Amendment of October,17, 2003, page 10).

The Patent Office is of the opinion that the specification does not describe the structure of Impurity II so that one of skill would have known that Impurity II has the structure of Formula I in which X_1 and X_2 are cholic acid groups and X_3 is a pentose monosaccharide group. The Office is also of the opinion that the specification does not describe the manner in which a cholic acid groups are attached to Impurity II; more particularly, that the cholic acid groups are attached to Impurity II in such a way that the terminal carboxylic acid group (CO_2H) is absent. Thus, the Office is of the opinion that undue experimentation would be required to determine how to make or use the compound claimed as Impurity II.

3. The claimed genus is enabled by the specification.

The issue at hand is whether the specification complies with the statutory requirement of 35 U.S.C. § 112 by describing 1) the structure of Impurity II to have the X_1, X_2 and X_3 groups as presently claimed; and 2) the manner in which the cholic acid groups are attached to the Impurity II, in such a way as to enable a skilled artisan to make or use the claimed compounds without undue experimentation. The issues raised in this rejection are the same as those made for the written description rejection and Appellants respectfully submit that the structure of Impurity II and the manner in which the cholic acid groups are attached thereto are fully supported by the specification based on Appellants' remarks presented in Part A of the present Appeal Brief.

Insofar as the Patent Office's allegation that "undue experimentation would be required to make or use the compound claimed as Impurity II" is applicable to the pending claims in light of the arguments presented above, Appellants respectfully disagree with the Patent Office.

a) The applicable legal standard for enablement.

To reject a claim for lack of enablement, the Patent Office must carry the initial burden to establish a reasonable basis for questioning the enablement provided by the specification. MPEP §2164.04. To satisfy the enablement requirement, the information contained in a patent specification must be sufficient to inform one skilled in the relevant art how to both make and use the claimed invention. *Id.* Whether the enablement requirement is satisfied depends on whether undue experimentation is necessary for one of skill in the art to practice the invention in light of the disclosure. *Id.*

The leading case regarding the sufficiency of the patent specification to support enablement under 35 USC § 112, first paragraph is *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As set forth by the Federal Circuit in *In re Wands*, multiple factors should be considered when determining whether any necessary experimentation is undue (*Id.* at 1404). These factors include:

(a) the breadth of the claims;

(b) the nature of the invention;

(c) the state of the prior art;

(d) the level of one of ordinary skill;

(e) the level of predictability in the art;

(f) the amount of direction provided by the inventor;

(g) the existence of working examples; and

(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

No single factor is determinative; rather, undue experimentation is a conclusion reached by weighing all the above noted factual considerations. *Id.* What is known in the art provides evidence as to the question of predictability. MPEP §2164.03. Applicants are not required to disclose every working example encompassed by their claims even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976). In fact "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ at 1404 (quoting *In re Jackson*, 217 USPQ 804 (B.P.A.I. 1982).

Appellants present analysis of claims 41, 54 and 55 in view of the factors set forth in *In re Wands*.

No Undue Experimentation Is Necessary to Practice the Claimed Invention

(1) The Breadth of the Claims

The amended claims are drawn to certain preferred embodiments of compounds having the structure of Formula I. Claim 41 is drawn to a compound having Formula I in which n is 3, X_1 and X_2 are both cholic acid groups, and X_3 is a pentose monosaccharide group. Claim 55 is drawn to a compound having Formula I in which n is 3, X_1 and X_2 are both cholic acid groups, and X_3 is a hexose monosaccharide group. Claim 54 is drawn to a specific compound that is within the claimed genus of compounds, namely 3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide.

The claimed genus is focused on certain preferred embodiments of the invention. In claims 41 and 55, the X_1 and X_2 groups are focused on only cholic acid groups, the X_3 group

is focused on only either a pentose or hexose monosaccharide, and the variable "n" is set to be only 3. In addition, claim 54 sets forth a single discrete compound that is within the scope of the claimed genus.

In view of the focused nature of the appealed claims, Appellants submit that the claim scope is clearly set forth and the claims are not overly broad or vague.

(2) The Nature of the Invention

The nature of the invention resides in the discovery that the novel impurities of Big Chap can enhance the delivery of therapeutic agents. The claims set forth certain preferred embodiments of the delivery enhancing compounds having the structure according to Formula I. The claimed compounds are organic molecules that can be prepared using reactions and techniques that are considered routine to one skilled in the art.

(3) The State of the Prior Art

The present invention relates to a class of delivery enhancing compounds that are related to Big Chap. Prior to the present invention, Big Chap was already recognized as a useful compound as evidenced by the commercial availability of Big Chap. The fact that Big Chap could be synthesized and sold on a industrial scale (commercial scale) indicates that the synthetic chemistry related to making Big Chap was well established.[3] What was not recognized until the present invention was that the novel impurities of Big Chap had delivery-enhancing properties that were far superior to Big Chap. However, Appellants submit that the state of prior art relating to the synthesis of Big Chap-type compounds was routine.

(4) The Level of Skill of One of Ordinary Skill

The present invention relates, in part, to the synthesis of organic compounds that are related to the known detergent, Big Chap. Organic synthesis is a well established and largely predicable art. In particular, the synthesis of compounds like Big Chap is well established. The present invention will be practiced most likely by scientists with advanced degrees (*e.g.*, Ph.D.

[3] In the Calbiochem product catalog, the following literature reference is cited as describing the synthesis of Big Chap: Hjelmeland, L. M, *et. al.*, "A New Class of Nonionic Detergents with a Gluconamide Polar Group.", Analytical Biochem., **1983**, 130, 485-490.

level chemists). As such, Appellants submit that the ordinary level of technical skill in this field is high.

(5) The Level of Predictability in the Art

The present invention describes the synthesis of organic compounds that are related to the known detergent, Big Chap. The predictability in the art refers to the ability of one skilled in the art to predict that the chemical reactions will proceed as planned. In the present case, the synthesis of Big Chap is known. The chemistry around the synthesis of Big Chap is known, and as such, the reactions used to make Big Chap (*i.e.*, attaching a cholic acid group to an amine, forming a mixed anhydride intermediate by reacting isobutylchloroformate and cholic acids) are well established reactions that provide predicable results. While small impurities arising from the synthesis of Big Chap (such as Impurity II) were not expected, they are the result from the reaction between the starting materials in a known manner, but in an unexpected and unpredictable stoichiometric ratio (e.g., cholic acid group and the amine react in a ratio of 2:1 when the reagents were combined in the reaction solution in a ratio of 1:1). Many of the same reactions used to make Big Chap are also used in the synthesis of the claimed compounds. Thus, Appellants respectfully assert that the predictability in the art, as it pertains to the synthesis of the claimed compounds is very high.

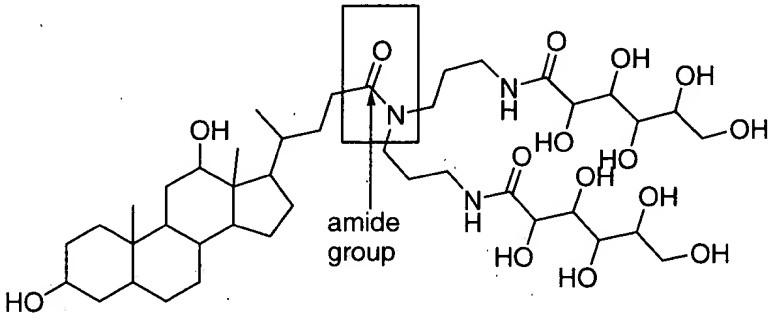
(6) The Amount of Direction Provided by the Inventor

The present application provides ample direction to practice the claimed invention. As stated earlier, the claims are now focused on a certain preferred genus of compounds in which X_1 and X_2 are now only cholic acid groups and X_3 is only a monosaccharide group (in particular, a pentose or hexose monosaccharide). The specification clearly teaches the preparation and use of a species (Impurity II) that is within the genus of compounds now claimed. In detail, the specification describes how Impurity II was isolated from Big Chap and synthesized in the laboratory (*see,* Examples 11 and 12). In addition, the specification provides guidance for analyzing Impurity II. For example, the specification provides mass spectral fragmentation information and Thin Layer Chromatography (TLC) analysis for Impurity II (*see*, Examples 11 and 12). The Patent Office alleges that the specification does not describe the structure of Impurity II to be as presently claimed. Appellants

respectfully disagree. As discussed in Part A of this Appeal Brief, the structure of Impurity II is readily apparent to a skilled artisan. Example 12 of the specification describes in great detail the synthesis of Impurity II, *i.e.*, the reagents used, the intermediates and final product formed. Thus, Appellants respectfully assert that the structure of the Impurity II is readily apparent to a skilled artisan.

The Patent Office is also of the opinion that the specification does not disclose that the cholic acid groups are attached at X_1 and X_2 in Formula I in a manner that gives the appearance that the terminal carboxylic acid groups (CO_2H) are removed. Again, for the reasons discussed in Part A of this Appeal Brief, Appellants respectfully. The specification provides a detailed description of the synthesis of Impurity II. Appellants respectfully assert that a skilled artisan would recognize that cholic acid is attached to Formula I to form an amide group. Additional evidence supporting Appellants' assertion of the manner in which the cholic acid group is attached to Formula I can be found in the chemical name of Impurity II. Example 12 teaches that the name of Impurity II is 3'-N-gluconamidopropyl-3"-N-***cholamido***propyl-N-***cholamide***. A skilled artisan would recognize from the name of Impurity II that the cholic acid group is attached via an ***amide*** group. As support, Appellants respectfully point out Big Chap is sold commercially under the name, N,N-*bis*-(3-D-Gluconoamidopropyl)deoxy**cholamide**. In the name of Big Chap, the "cholamide" group refers to a cholic acid group in Big Chap wherein the carboxylic acid group of cholic acid is replaced with an amide group. The structure of Big Chap is shown below (*see*, Figure 6).

Figure 6



N,N-*bis*-(3-D-Gluconoamidopropyl)deoxy**cholamide**

"Big CHAP"

In view of the above, Appellants submit that the specification provides significant amount of guidance for making and using the claimed invention.

(7) The Existence of Working Examples

The specification provides a working example for making a compound within the claimed genus. As stated earlier, the claims are now focused on certain preferred genus of compounds in which X_1 and X_2 are now only cholic acid groups and X_3 is only a monosaccharide group (more particularly a pentose or hexose monosaccharide). The specification clearly teaches the preparation and use of a species (Impurity II) that falls within the genus of compounds now claimed. Appellants assert that even a single species is sufficient to claim a genus as a whole. MPEP § 2163 sets forth:

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. **On the other hand, there may be situations where one species adequately supports a genus.** (Emphasis added)

(8) The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure.

The claims on appeal are now focused on a certain preferred genus of compounds in which X_1 and X_2 are only cholic acid groups and X_3 is only a monosaccharide group (in particular a pentose or hexose monosaccharide). Again, as the specification already teaches how a cholic acid group is attached to Formula I. X_3 is a monosaccharide group and Appellants submit that carbohydrate chemistry is a well established art and thus finding suitable experimental conditions to attach other monosaccharide groups would be simply routine procedure. "The test [of undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 190 USPQ 214, 217-19, (CCPA 1976)).

In the instant case, any necessary experimentation for practicing the claimed invention would be routine for an ordinarily skilled artisan who is familiar with the well

established techniques of chemistry. As such, Appellants submit that beyond the teaching provided in Example 12, very little routine experimentation would be required to make or use the invention.

4. Summary

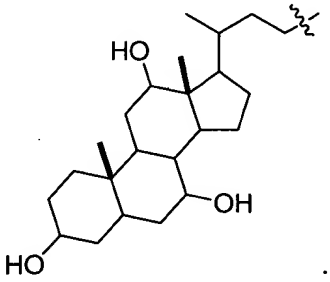
The specification provides considerable direction and guidance on how to practice the invention and presents a working example. Accordingly, Appellants respectfully submit the rejection of claims 41 and 55 under 35 U.S.C. § 112 is improper and should be withdrawn.

C. The rejection of claims for being indefinite is improper.

The Patent Office has rejected claims 41 and 55 under 35 U.S.C. § 112, second paragraph, as being indefinite as allegedly the claim is unclear with regard to how the cholic acid group is attached to Formula I. Appellants respectfully traverse the rejection.

The Patent Office alleges that the addition of cholic acid to Formula I may result in 1) building 4 carbon atoms between the carboxyl group and the pentose ring of cholic acid; 2) removal of the carboxyl group of cholic acid; or 3) attachment of cholic acid to Formula I *via* one of the hydroxyl groups. The Office alleges that it is unclear whether Appellants intend the claim to encompass any means of attaching cholic acid to Formula I at X_1 and X_2 or if the claim is limited to the removal of the carboxyl group on cholic acid. Appellants respectfully traverse the rejection.

Claims 41 and 55 clearly sets forth that the cholic acid group attached to Formula I has the following structure:



The connectivity of the cholic acid groups to Formula I as shown in the claims is supported by Example 12 which teaches the synthesis of Impurity II, a compound of the present invention. Appellants respectfully assert that the connectivity of the cholic acid groups is readily

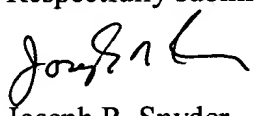
apparent to a skilled artisan based on the description of the synthesis of Impurity II in Example 12 and from the name of Impurity II. As discussed in Part A of the present Appeal Brief, Appellants respectfully assert that based on the synthetic procedure provided in Example 12, which describes the reaction of a mixed anhydride of cholic acid with an amine (3-aminopropyl-3'-N-gluconamidopropyl-amine), a skilled artisan practicing the present invention would readily recognize that the cholic acid group is attached in Impurity II in a manner that gives the appearance that the carboxylic acid group is removed (*i.e.*, the second option presented above by the Patent Office). Moreover, as discussed in Part B of the present Appeal Brief, the name of Impurity II, "3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide" clearly indicates that the cholic acid group has been incorporated in an "*cholamido*" and in an "*cholamide*" group. One skilled in the art would readily recognize that *"cholamido"* or *"cholamide"* means that the cholic acid has been incorporated into Formula I as part of an amide group. Of the three scenarios presented by the Examiner for attaching a cholic acid group to Formula I, the only option that would make chemical sense results in the integration of the cholic acid group into Formula I as a "cholamido" group as is presently taught and claimed is option 2. This gives the appearance that the carboxylic acid group of cholic acid is removed.

In view of the amendment to the claims, Appellants submit that the claim is clear with regard to how the cholic acid group is attached to Formula I. As such, Appellants respectfully request the rejection under 35 U.S.C. § 112, 2nd paragraph be withdrawn.

In summary, Appellants submit that present application and claims fully satisfy the statutory requirements of 35 U.S.C. § 112, first and second paragraphs. Appellants respectfully urge the Board to withdraw all the rejections against the pending claims (*i.e.*, claims 41 and 54-55) and send the application to issuance.

If for any reason, the Board believes a telephone conference would expedite resolution of the Appeal, the Board is invited to telephone the undersigned at 925-472-5000.

Respectfully submitted,



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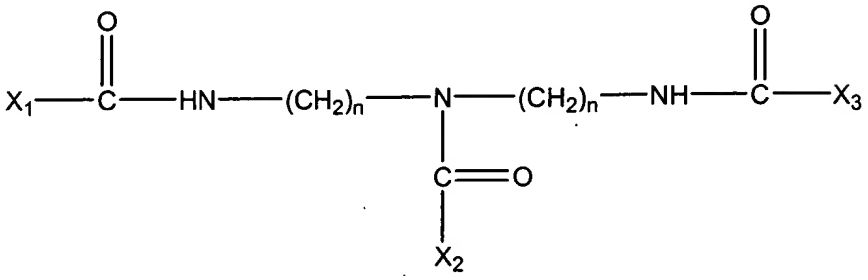
JS:sc
60427675 v1

CLAIMS APPENDIX A

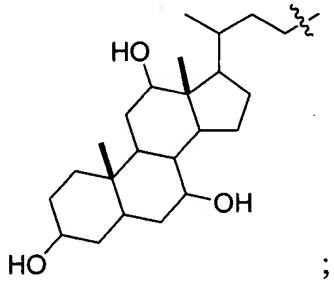
41. (Previously presented) A compound of Formula I:



wherein:

n is 3;

X_1 and X_2 are both cholic acid groups; wherein the cholic acid group has the formula:



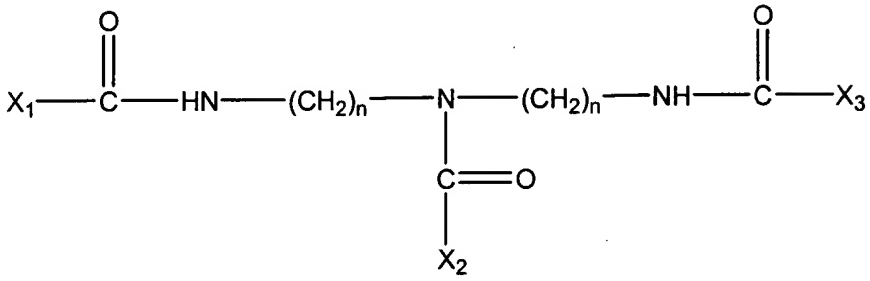
;

and X_3 is a pentose monosaccharide group.

54. (Previously presented) A compound having the formula:

3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide.

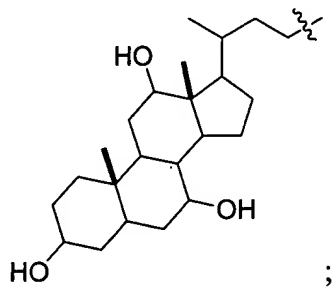
55. (Previously presented) A compound of Formula I:



wherein:

n is 3;

X_1 and X_2 are both cholic acid groups; wherein the cholic acid group has the formula:



;

and X_3 is a hexose monosaccharide group.

EVIDENCE APPENDIX B

Below are the Appendices filed with the present application. Appendix B1 is a reproduction of Figure 20 that was originally filed with the instant application. Appendix B2 was first provided in an amendment filed on July 13, 2004 and again on September 2, 2004; and entered in the record as acknowledged by the Examiner in the Non-Final Office Action of November 2, 2004.

Appendix B1: Figure 20

Appendix B2: Heathcock, C. H., *et. al.*, "Introduction to Organic Chemistry"

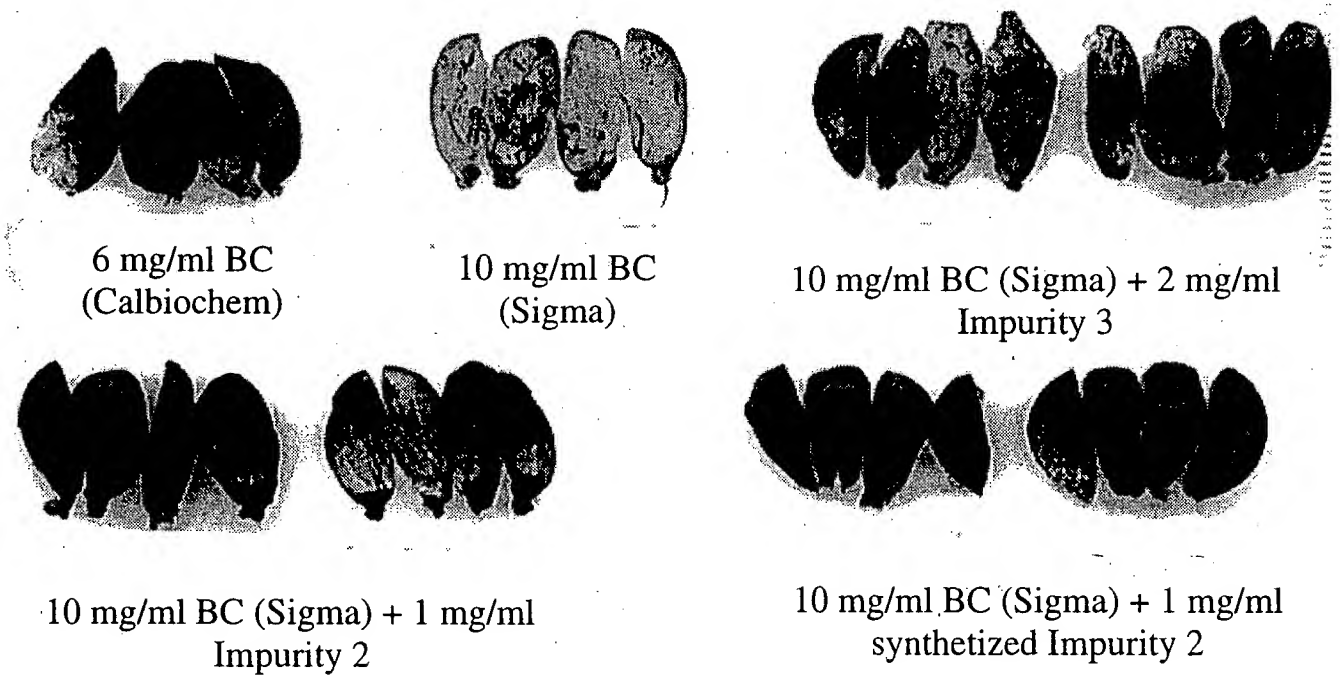


Figure 20 **Improved Gene Transfer after Spiking of Impurities II or III into BC - Sigma**

INTRODUCTION TO ORGANIC CHEMISTRY

FOURTH EDITION

REVISED PRINTING

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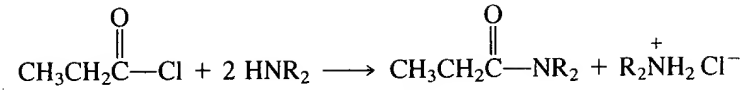
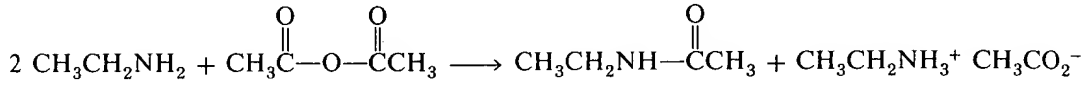
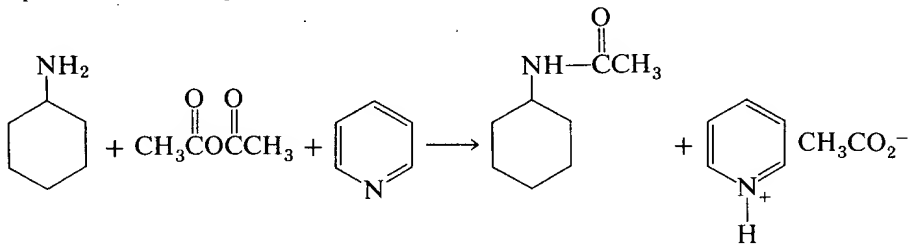


(R = H or alkyl)

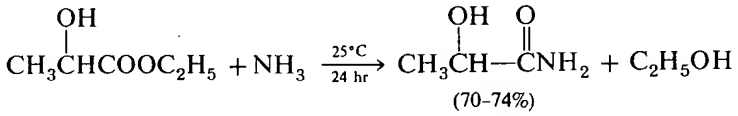
The reaction of ammonia and amines with anhydrides follows a similar course; the products are 1 mole of amide and 1 mole of carboxylic acid. Since the liberated acid reacts to form a salt with the ammonia or the amine, it is necessary to employ an excess of that reactant.



As in the analogous reaction of amines with acyl halides, one may carry out the reaction in the presence of one equivalent of tertiary amine.



Esters also react with ammonia and amines to yield the corresponding amide and the alcohol of the ester. This synthetic path is useful in cases where the corresponding acyl halide or anhydride is unstable or not easily available. An interesting example of such a case is



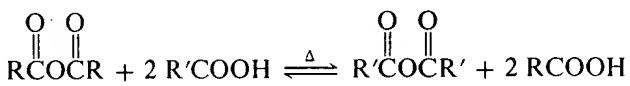
(70–74%)

In this case the acyl halide method for preparing the amide may not be used, since the molecule contains an OH group, which will react rapidly with an acyl halide.

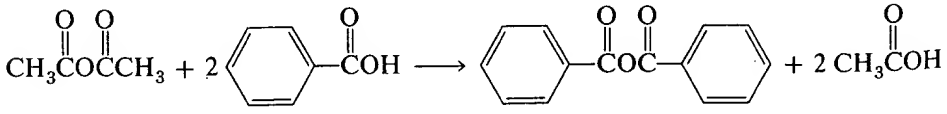
EXERCISE 19.7 Treatment of 2-hydroxypropanoic acid (lactic acid) with thionyl chloride gives a product having the formula $C_6H_8O_4$. Propose a structure for this material.

C. Reaction of Acyl Halides and Anhydrides with Carboxylic Acids and Carboxylate Salts. Synthesis of Anhydrides

A mixture of an acid anhydride and a carboxylic acid undergoes equilibration when heated.



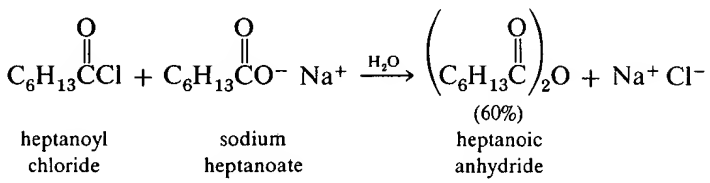
The reaction is preparatively useful when the anhydride is acetic anhydride. In this case, acetic acid can be removed by distillation as it is formed because it is the most volatile component in the equilibrium mixture.



(72–74%)

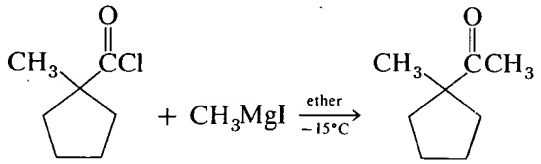
b.p. 142°C — benzoic acid — benzoic anhydride — b.p. 117°C

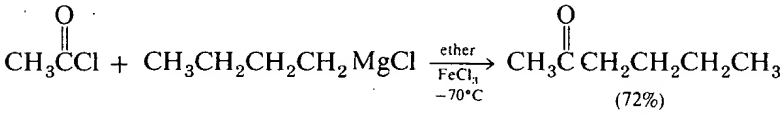
The only carboxylic acid derivatives that undergo a useful reaction with carboxylate salts are acyl halides. The product is an anhydride.



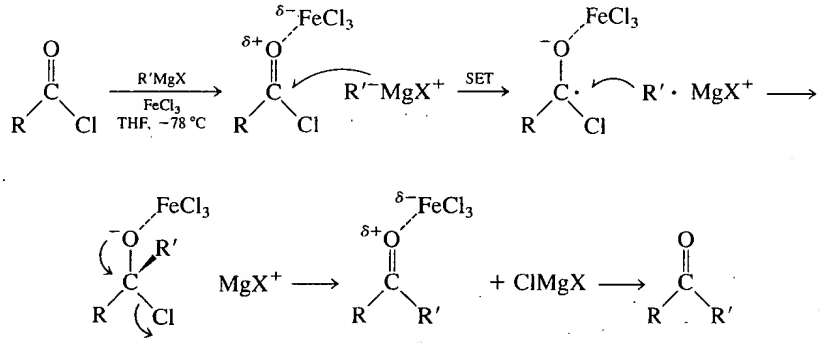
D. Reaction with Organometallic Compounds

Acyl halides react with various organometallic reagents to give ketones. Since ketones are also reactive towards many of the reagents, it is best to use less reactive agents when the target compound is the ketone. Reaction with a Grignard reagent can give ketones if the reaction is carried out at low temperature and the Grignard reagent solution is added to the acyl halide to avoid further reaction of the ketone to form tertiary alcohol. Anhydrous ferric chloride is often added as a catalyst.





Ferric chloride may serve as a Lewis acid, complexing with the oxygen of the acyl chloride. Many organometallic reactions are now thought to proceed by **single electron transfer (SET).** The carbanion of the Grignard transfers an electron to the acyl chloride–ferric chloride complex to yield a stabilized radical anion and a highly reactive alkyl radical. The radical then combines with the radical anion to form the "tetrahedral intermediate" familiar from our discussion of hydrolysis. The intermediate decomposes to yield the ketone, magnesium halide and the catalyst ferric chloride.



(See Sections 8.6 and 8.8.) Rapid reaction at low temperatures is consistent with an SET mechanism.

If excess Grignard reagent is used the product ketone reacts further, giving a tertiary alcohol.

RELATED PROCEEDINGS APPENDIX C

None